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TYPES OF HUMAN DIABETES*

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The twin sisters clinical observation and laboratory experiment have walked, in the field of diabetes, very closely hand in hand. Sometimes one has led, sometimes the other. But whichever led, the second soon proceeded to further progress, to their mutual benefit and stimulation. We clinicians must gratefully acknowledge that the experimental side has far outstripped ours in the last 15 years, and the animal investigations of Houssay, Young, and others have clearly shown the importance of pituitary and adrenal hormones in the regulation of carbohydrate metabolism and the production of diabetes. This confirms our suspicions that the term "diabetes mellitus" includes a variety of glycosuric conditions separate both in clinical type and in aetiology. I shall try to subdivide these.

The Greeks described the syndrome of "diabetes" as "a melting of flesh into water"; a sweet honeyed substance, "mellitus," was shown to be present by Willis in England in 1672; the more precise measurements of modern science have shown a fundamental hyperglycaemia as well as glycosuria and a frequent ketonuria in relation to the classical syndrome of thirst, polyuria, loss of weight, and erstwhile resultant coma. But I should point out that many diabetics never develop ketosis and that many of these remain obese, and it is largely on these two features that I shall attempt to differentiate clinical types. More fundamentally I suggest that diabetics can be divided into those who probably are not insulin-deficient and others who certainly are. I have coined words to categorize some types with clarity. These words have also, I believe, a sound Greek origin.

Methods of Experimental Diabetes

Before passing to man and to the consideration of clinical types, I think it useful to summarize the various experimental procedures which have been proved to produce true severe diabetes or merely glycosuria and mild disturbances of carbohydrate metabolism in animals. In the Table these are arranged mainly in historical order, and need not be explained in detail. Nos. 6, 7, and 8, though causing glycosuria, hardly merit inclusion as diabetes. It is obvious that all clear-cut patterns of

Experimental "Diabetes"

Produced by	Mode of Action
I. Pancreatectomy	Islet lack
II. Anterior pituitary extracts (Young):	
(*a*) Young's = growth hormone	Islet destruction
(*b*) A.C.T.H.	Through cortisone
III. Alloxan	Islet destruction
IV. Glucose injections	Islet destruction
V. Suprarenal:	
(*a*) Cortisone	?
(*b*) Adrenaline hyperglycaemia	Glycogenolysis
6. Thyrogenic hyperglycaemia	Glycogenolysis
7. Claude Bernard's puncture	? Hypothalamic; brief glycogenolysis
8. Phloridzin "diabetes"	Low renal threshold

experimental diabetes (I to IV) arise from total destruction of the pancreas or specific damage to the islet, resulting in insulin deficiency.

Types of Human Diabetes

The vast majority of human diabetics—and these interest me most—show no clear aetiological analogy to the above experimental forms. But certain rare cases are clearly due to primary pancreatic disease which destroys insulin production, and to other endocrine factors which induce a diabetic state. I shall enumerate these briefly before passing to the commoner types.

Primary Pancreatic Destruction.—(*a*) Total surgical pancreatectomy for widespread carcinoma or hyperinsulinism; (*b*) calculus disease and chronic relapsing diabetes; (*c*) haemochromatosis (these three forms are severely insulin-deficient); and (*d*) chronic fibrosis, often with steatorrhoea, in which the diabetes is mostly mild, but sometimes needs insulin.

Primary Disturbance of Other Endocrines.—(*a*) Pituitary: (1) Acromegaly; severe diabetes. (2) Cushing's basophilism; milder. (*b*) Adrenal disease: (1) Phaeochromatoma; variable severity. (2) Basophilism; variable severity. (*c*) Thyrogenic diabetes (?).

With Disturbances of Fat Storage.—There are two clinical conditions in which diabetes is most clearly associated with a lack or an excess of depot fat: they have no analogies in animal or experimental work. For these conditions I have coined the words "lipoatrophic" and "lipoplethoric" diabetes respectively.

Lipoatrophic Diabetes

This is, I think, a suitable term for an extremely rare condition, a case of which, after seven years' study, I published in detail (Lawrence, 1946) and shall summarize

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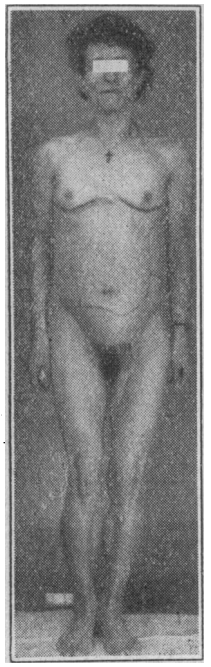

FIG. 1.—Case of lipoatrophic diabetes. Reproduced from the *Lancet*, 1946, 1, 724.

here, as it is essential to my argument and speculations. I would point out that this condition has nothing in common with the frequent type of severe wasting diabetes, later described, in which fat stores are quickly replenished by insulin treatment.

Fig. 1 shows this woman aged 30 (normally adipose four years before) with no fat four years after the onset of "diabetes." Post-mortem examination showed no depot fat, perirenal or elsewhere, an enormous portally cirrhosed liver, a huge spleen, but a completely normal histological picture in all endocrine glands, including the pancreas.

Metabolic studies revealed n extraordinary condition. A high blood and urinary sugar, requiring 2,000 units daily for control, was never accompanied by ketosis even when insulin was reduced or omitted. But all phases of hyperglycaemia produced an intense lipaemia, 4 to 8%, quite independent of various levels of dietary fat and carbohydrate. This lipaemia repeatedly disappeared when hyperglycaemia was controlled by vast doses of insulin (1,600 to 2,000 units daily), but there was no appreciable change in subcutaneous fat.

Two similar published cases (Hansen and McQuarrie, 1940; Ziegler, 1928)—one of which is illustrated in Fig. 2—show that the extraordinary lipoatrophic case I have described has a metabolic lesson—namely, that "diabetes" can result when fat cannot be stored. Its meaning is discussed in relation to the contrast of the next type.

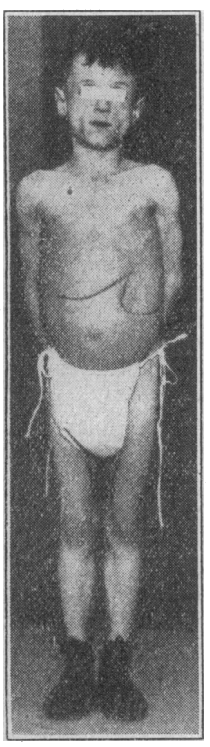

FIG. 2.—Hansen and McQuarrie's case. Reproduced from *Proc. Soc. exp. Biol., N.Y.*, 1940, **44**, 611.

Lipoplethoric Diabetes

This again, I think, is a suitable term to describe the contrast in excessive fat storage which is associated with the commonest type of diabetic patients who crowd our clinics and practices—middle-aged obese men, and particularly women at or soon after the menopause (Fig. 3). Female diabetics of this type now exceed the males by 2 to 1 among all civilized and well-nourished peoples. This sex distribution is quite different from that in England at the beginning of this century, when male diabetics of all types exceeded the females. I cannot believe that inborn genetic factors have changed in the last 25 years, and would ascribe the vast increase in obese female diabetics to a relative abundance of food. Long ago the altruistic working-class woman was relatively starved. Now she has an abundance of bread, potatoes, and other foods, so she gets fat and develops this type of diabetes. Perhaps this is too simple an explanation, but it is supported by the virtual disappearance of lipoplethoric diabetes in starved Germany in 1917–18 and its occurrence in Bengal only among those who are rich enough to get fat. At any rate, large numbers of these obese diabetics present with some thirst, with pruritus, with hyperglycaemia and intense glycosuria, but with *no ketosis*. When treated with diets low in carbohydrate and low caloric values in protein and fat to reduce their weight substantially, the diabetes practically disappears, and even the glucose-tolerance test may become normal. A relapse occurs when dieting is relaxed sufficiently for weight to be regained, but is readily overcome by further restriction. I think it bad treatment to prescribe insulin and liberal diets in such cases, as this prevents the reduction in weight which I consider essential. Such cases are relatively insensitive to insulin.

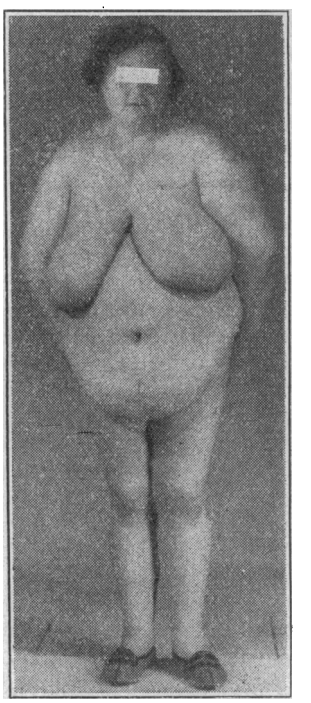

FIG. 3.—Case of lipoplethoric diabetes.

A likely explanation of these two types of diabetes, in which a similar state of hyperglycaemia without ketosis is associated with opposite states of fat storage, can be based on tracer experiments which show what the end-action of insulin on carbohydrate is in relation to fat storage. Insulin turns labelled glucose not only into glycogen but, almost equally rapidly, into stored fat. Indeed, acting on a large meal, insulin is quantitatively more lipogenic than glycogenic. The lipoatrophic subject cannot store fat, and therefore cannot store ingested sugar, which circulates in excess. Perhaps the overfull stores of the lipoplethoric patient prevent the easy storage of sugar, though this latter explanation may be too facile. In any case, I suggest that these types of diabetes are due not to insulin deficiency but to lack of an unknown hormone and/or enzyme system concerned with the regulation of storage of fat. I have elsewhere called this the "lipopexic" factor, but the contrasting conditions might equally well depend on an excess or a deficiency of a thinning or "lipocatabolic" factor. Such speculations have no substantial evidence to support them, and certainly they have no experimental foundation. But perhaps, in this field, clinical observation may lead to a later experimental approach.

Insulin-deficient Diabetes

This well-known severe type presents the most difficult problems for the clinician both in its treatment and in the obscurity of its aetiological factors. In contrast to previous types, the characteristic feature is the *ketosis* which accompanies the hyperglycaemia and which, in

the absence of insulin treatment, leads to coma. Ketosis occurs whenever little or no carbohydrate is available for use and the body has to metabolize fat instead, and in diabetes it is a direct indication that there is little or no insulin production to make the excess sugar available.

All diabetic children, and most adults under 40 and many over 70, are of this type, whereas lipoplethoric diabetes predominates between the ages of 45 and 60. They need insulin treatment badly, are sensitive to it, and owe their lives to its continuous use.

Sometimes the disease is controlled at first by quite small doses of insulin—indeed, it may be given up for a time—but as months and years go on the majority become stabilized at insulin requirements of some 35 to 60 units a day. This requirement remains fairly constant, though at different levels in different patients, except when complicating conditions or illnesses occur. For years I have regarded the state as one of *absolute diabetes* in which the islets are producing no appreciable insulin; but this has not been proved. They certainly behave as if they secrete no endogenous insulin. Immediately the activity of an injection is exhausted hyperglycaemia and ketosis resurge even more quickly than the next dose of insulin removes them.

There are difficulties in the treatment of these insulin-deficient subjects, because no type of injected insulin can imitate or produce the physiological pattern of normal carbohydrate metabolism. Many are unstable for social reasons, but all uncomplicated cases should, and most do, achieve a normal life of work and play for many years if they receive suitable treatment.

Because this severe type seems ultimately to be due to insulin deficiency, it does not follow that the primary cause is an inherent pancreatic weakness. An important factor in islet destruction is a continuous hyperglycaemia, and experiment has shown that if this is maintained it can destroy the islets of healthy cats. If it is prevented by insulin or low carbohydrate diets, the diabetogenic pituitary factor of Young does not produce the usual diabetes. The early studies of Allen on dogs and human diabetics also showed that if hyperglycaemia could be prevented by diet the progress of the disease would be stayed or minimized; and widespread clinical experience, including my own, supports this. Continuous hyperglycaemia seems essential in the production of severe grades of islet destruction. But we know from experimental work that hyperglycaemia can be initiated by extrapancreatic hormonal factors, and human diabetes may well begin in the same manner. At the moment the pituitary and the hypothalamus are the most fashionable hypothetical factors. There is, however, no factual evidence to support this theory, and I would point out that cases of insulin-deficient diabetes occur in all types and races and show no clear signs, either physical or mental, of any other endocrine dysfunction. The mystery of their origin is still profound.

Nor does consideration of the undoubted hereditary factor in diabetes help to clarify the aetiological puzzle, and the nature of transmission, recessive or more complicated, remains obscure. But Harris's (1949, 1950) analysis of over a thousand cases from King's College Hospital at least suggests that the lipoplethoric and the insulin-deficient type tend to run separately in families and may be due to separate genetic influences.

Vascular Complications of Diabetes

One thing that is common to all types of diabetes is the tendency of long-standing cases to develop similar vascular complications—retinopathy, albuminuria, renal sclerosis, and undue occlusion of vessels in the feet (gangrene) and in the coronary and cerebral systems. Twenty years ago I taught students that only the long-standing lipoplethoric type developed these complications, but insulin has kept other types alive long enough for them also to develop the same disastrous complications. These have been observed in diabetes due to haemochromatosis and to relapsing pancreatitis, and the lipoatrophic case described above showed, after eight years, typical commencing intercapillary changes in the kidney glomeruli. Is this an indication that hyperglycaemia, apart from type and nutritional state, is the prime factor causing these vascular changes?

Further Investigations

I have described different types of human diabetes on grounds of clinical experience and observation, but I know that my speculation on their aetiology rests on no very sound basis. Further investigations are required in two directions which are very difficult in human diabetes: first, the histology of the islet cells and the insulin content of the pancreas of these types should be compared in very fresh post-mortem material; and, secondly, the difficult estimation of blood insulin in various types would give the clearest answer, and seems to be near realization. The method of Bornstein (1950) with hypophysectomized, adrenalectomized alloxan-diabetic rats appears to be the most promising.

And so, in the near future, the different types I have described may be put on a firm basis of experimental proof. I may be shown to be partially right or entirely wrong, but this hardly matters if I have been able to give a stimulus to present thought and future knowledge.

Summary

Human diabetics are divided clinically into two main types: (1) those who probably are not insulin-deficient, and (2) those who certainly are.

The former type, again, is divided into two, depending on the absence or excess of fat stores, and the new words lipoatrophic and lipoplethoric diabetes have been coined to describe them.

REFERENCES

Bornstein, J. (1950). *Aust. J. exp. Biol. med. Sci.*, **28**, 87, 93.
Hansen, A. E., and McQuarrie, I. (1940). *Proc. Soc. exp. Biol., N.Y.*, **44**, 611.
Harris, H. (1949). *Proc. R. Soc. Med.*, **42**, 326.
—— (1950). *Ann. Eugen., Camb.*, **15**, 95.
Lawrence, R. D. (1946). *Lancet*, **1**, 724, 773.
Ziegler, L. H. (1928). *Brain*, **51**, 147.

In his annual report for 1949, Dr. C. Fraser Brockington, county medical officer of the West Riding of Yorkshire, estimates that the cost of treating patients with diphtheria in the West Riding is now £75,000 less each year than it was between 1935 and 1939. Over and above this there is a saving represented by the nurses and domestic workers previously needed for the 256 beds which are no longer occupied: this is estimated to be £53,600 per year. According to the estimates of the cash value of a human life made by economists and actuaries, the estimated value of the lives saved is about £43,000 a year. The total annual saving, therefore, amounts to £172,000 a year. Against this is the cost of diphtheria immunization—about £10,000 a year. "The monetary saving of this single operation in preventive medicine therefore exceeds by £10,000 the estimated cost for 1950–1 of the whole of the health-visiting service (in the West Riding)."